FUNDAMENTAL VIROLOGY

Third Edition

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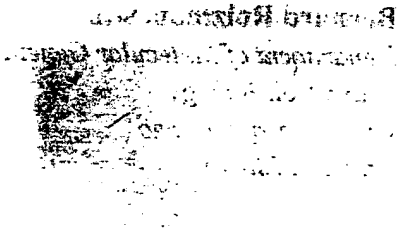

lentiviruses are illustrated in Fig. 2 (292). Simian immunodeficiency virus has also been isolated from several Asian macaque species held in captivity in primate research facilities in the United States; these viruses include SIV from rhesus macaques (SIV_{MAC}), nemestrina macaques (SIV_{MNE}), and stump-tailed macaques (SIV_{STM}) (229). Each of these viruses causes a fatal AIDS-like disease in several macaque species (390). Because the various macaque viruses are all closely related to SIV_{SMM}, it appears that captive macaques were inadvertently infected either by cohousing Asian macaques and African monkeys (i.e., sooty mangabeys) and/or through experimental inoculation of macaques with fluids and other materials from African monkeys. Despite extensive sequence diversity, a unifying feature of human and nonhuman primate lentiviruses is that the cell receptor is the CD4 antigen, a differentiation marker on the surface of T-helper lymphocytes (784). A compendium of HIV and SIV sequence information, based on extensive analysis of numerous viral clones, is found in the database prepared by Myers et al. (519). At present, the origins of HIV-1 and HIV-2 infections remain an enigma, although it is possible that both of these viruses arose from zoonotic transmissions between nonhuman primates and humans (188).

VIRAL GENOME STRUCTURE AND ORGANIZATION

Infectious virions of HIV and SIV contain two identical copies of single-stranded RNA, about 9.2 kb long, that have positive polarity with respect to translation. In the early stages of infection, the virion RNA genome is converted into double-stranded linear DNA by the process of reverse transcription [via viral-encoded reverse transcriptase (RT)], which involves two strand-transfer steps to synthesize linear viral DNA with long terminal repeats (LTRs) flanking viral genes (Fig. 3). This linear viral DNA is integrated into the host cell genome to produce the provirus. Accordingly, HIV and SIV, like other retroviruses, have two genomic forms: single-stranded RNA in the extracellular phase of the viral life cycle (i.e., virions) and double-stranded DNA (i.e., provirus) within the cell. Genomic viral RNA is synthesized by cellular RNA polymerase II from proviral DNA and thus contains a cap structure at the 5′ end and a poly-A tail at the 3′ end. Generic features of both the RNA and DNA forms of retroviral genomes are described in detail in Chapter 26 in this volume.

Both HIV and SIV encode precursor polypeptides for virion proteins as well as several additional open reading frames (Fig. 2 ; and Table 1). The *gag* gene encodes the precursor for virion capsid proteins, the *pol* gene encodes the precursor for several virion enzymes [protease (PR), RT, RNase H, and integrase (IN)], and the *env* gene encodes the precursor for envelope glycoprotein (Env gp). The transcriptional transactivator (*tat*) and regulator of viral expression (*rev*) genes are each encoded by two overlapping exons and produce small nonvirion proteins which are essential for viral replication. Both HIV and SIV also encode several genes which are nonessential (i.e., dispensable) for viral replication in tissue culture cells. Nonessential genes, also designated "accessory" or "auxiliary" genes, encoded by HIV-1 are *vif, vpr, vpu,* and *nef*; HIV-2 and SIV encode *vif, vpx* and/or *vpr,* and *nef.* Pro-

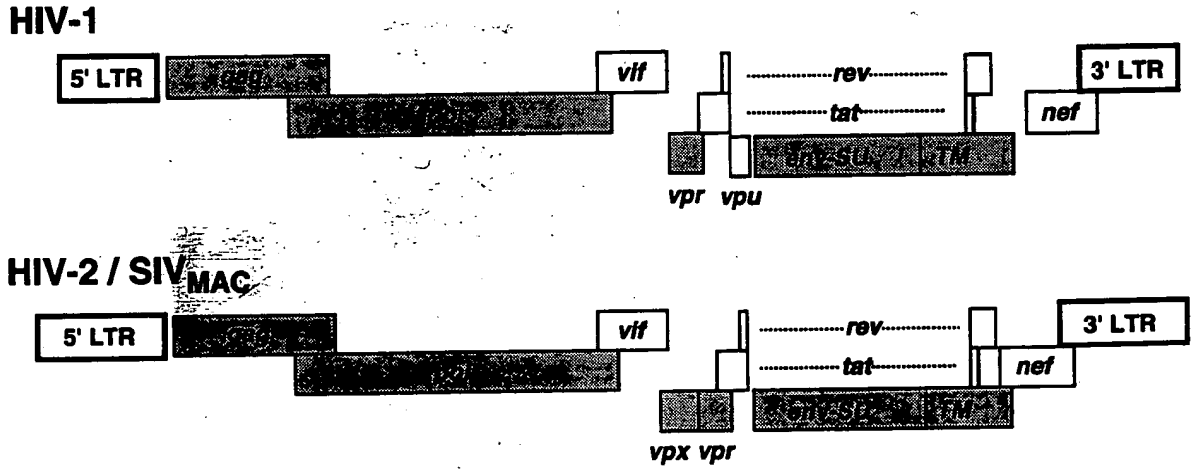

FIG. 3. Genome organization of primate lentiviruses. The linear double-stranded proviral DNA forms of HIV-1 and HIV-2/SIV_{MAC} show similar patterns of genomic organization. Structural genes (*gag, pol,* and *env*) are heavily shaded. Accessory genes, including essential regulatory genes (*tat* and *rev*), and nonessential genes (*nef, vif, vpu, vpx,* and *vpr*), are lightly shaded. (For viral gene nomenclature, see Table 1.) The 5′ and 3′ LTRs flanking viral genes are shown as open boxes. *Vpu* is found exclusively in HIV-1, whereas *vpx* is found only in HIV-2 and certain strains of SIV. *Vpr* is encoded by both HIV-1 and HIV-2/SIV_{MAC} (see text).

TABLE 1. *Genes and proteins of primate lentiviruses*

Gene[a]	Dispensable for Replication	Protein	Function	Localization
gag	No	$Pr55^{gag}$	Polyprotein precursor for virion core proteins MA (p17), CA (p24), NC (p9), p7	Virion nucleocapsid
pol	No	$Pr160^{gag\text{-}pol}$	Polyprotein precursor for virion enzymes PR: p10, RT and RNAse-H: p51/66, IN: p32	Virion (nucleocapsid?)
vif	Yes[b]	p23	Viral infectivity factor, function unresolved	Cell cytoplasm
vpx[c]	Yes	p16	Virion protein, function unresolved	Virion
vpr	Yes	p15	Virion protein, function unresolved	Virion
tat	No	p14	Transcriptional transactivator, binds TAR and cell factor(s) (initiation and elongation of viral transcripts)	Primarily in cell nucleus
rev	No	p19	Posttranscriptional transactivator, binds RRE and cell factor(s) (splicing and/or transport and translation of viral mRNA)	Primarily in cell nucleus
vpu[d]	Yes	p16	Influences virus release, augments turnover of CD4 antigen	Integral cell membrane protein
env	No	gp160	Precursor for envelope glycoprotein: SU (gp120): CD4 receptor binding, TM (gp41): membrane fusion	Virion envelope, plasma membrane
nef	Yes	p27	Negative effector?, downregulates CD4 receptor, influences T-cell activation, enhances virion infectivity	Cell cytoplasm, plasma membrane

[a] Gene nomenclature is based on that in Gallo et al. (222).
[b] Dependent on cell type.
[c] Encoded only by HIV-2 and several SIV strains (see text).
[d] Encoded only by HIV-1 and SIV_{CPZ}.
MA, matrix protein; CA, capsid protein; NC, nucleocapsid protein; PR, protease; RT, reverse transcriptase; IN, integrase; SU, surface glycoprotein; TM, transmembrane protein; TAR, tat-response element; RRE, rev-response element; HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus.

teins produced from the *vpr* and *vpx* genes are assembled into virions, whereas the *vif, vpu,* and *nef* gene products appear not to be packaged into virions.

As a group, the proviral genomes of primate lentiviruses display a high content of adenosine deoxyribonucleotide (A) residues (38% to 39%) and a low frequency of cytidine deoxyribonucleotide (C) residues (16% to 19%). The preference for A residues is a feature of all lentiviruses (517). The generation of a A-rich viral genome may be due to an enzymatic property of RT (see section on reverse transcriptase) and/or selective pressure during evolution of the virus group. For example, the strong bias in the *env* gene for the triplet AAT and related codons favors serine, threonine, and asparagine; this bias appears to lead to the creation of new N-linked glycosylation sites, which could enable the virus to escape from the host immune response (62). A consequence of the high frequency of A-rich triplets is that HIV and SIV codon usage differs dramatically from that of cellular genes (52,388).

VIRION STRUCTURE

Models for the structure of HIV and SIV virions are based on a combination of high-resolution electron microscopy of viral particles and both biochemical and immunochemical analyses of virion components (233,514). By these approaches, extracellular particles produced by cells infected with HIV-1, HIV-2, and the various SIV strains are very similar in morphology and composition. Virions have a spherical shape, are about 110 nm in diameter, and consist of a lipid bilayer membrane or envelope that surrounds the cone-shaped nucleocapsid (Figs. 1 and 4). Although the overall shape of virions is spherical, computer simulation of shadowed replicas and photomicrographs produced by scanning electron microscopy suggest that virions are icosadeltahedrons (465,527). Each nucleocapsid is about 100 nm in the long dimension and spans the entire diameter of the virion. Analysis of electron micrographs by computer-imaging techniques reveals a nucleocapsid with a wide free end, 40 to 60 nm across, and a narrow end, about 20 nm in width. This narrow end of the nucleocapsid appears to be connected to the lipid bilayer through a proteinaceous structure designated the core (capsid)-envelope link (CEL) (298). The region between the viral envelope and the electron-dense nucleocapsid has been termed the paranucleoid region, core shell, or lateral body (823). The composition of both the CEL and the paranucleoid region remains to be determined. Although spherical virions with one nucleocapsid are the major forms released from infected cells, a small percentage of extracellular particles contains two or more spherical capsids, and tubular capsids, 40 to 200 nm long, have also been ob-